Functional Segregation of ITD Sensitivity in the Inferior Colliculus of Decerebrate Cats

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The location of a sound originating off the median plane can be derived from interaural time differences (ITDs) that reflect the unequal distance traveled by the sound to reach the two ears (Wightman and Kistler 1992). A pathway for processing this temporal information is established when ascending sound representations from each ear converge on binaurally sensitive neurons in the superior olivary complex (Irvine 1986, 1992; Oliver and Huerta 1992). Neurons from the superior olive send excitatory projections to the central nucleus of the inferior colliculus (ICC) where binaural temporal information presumably because their dominant ascending inputs arise from weakly binaural neurons in the dorsal cochlear nucleus.

**INTRODUCTION**

The ITD selectivity of single-unit responses in the superior olive is determined by the conduction delay properties of neurons that convey discharge rates to the binaural brain stem. Most MSO neurons are designated “peak units” because they produce pure-tone ITD functions that show a maximum response (peak) at the same time disparity regardless of stimulus frequency (Batra et al. 1997; Caird and Klinke 1983; Guinan et al. 1972a,b). Consequently, LSO neurons respond minimally when binaural inputs are coincident (Batra et al. 1997; Caird and Klinke 1983; Finlayson and Caspary 1991). The ITD selectivity of single-unit responses in the superior olive may simply reflect the heterogeneity of brain stem responses because their spatial receptive fields are primarily determined by interaural level differences cues (Tollin and Yin 2002a,b). Most LSO neurons are classified as “trough units” because their ITD frequency functions coincide at the minimum response (trough).

Neurons from the superior olive send excitatory projections to the central nucleus of the inferior colliculus (ICC) where they intermingle with excitatory and inhibitory inputs from a broad array of sources (Irvine 1986; Oliver and Huerta 1992). In spite of this highly convergent innervation, the majority of binaural temporal responses in the ICC can be explained by the sensitivity of their ascending inputs (Cai et al. 1998). Not surprisingly, most ICC neurons show peak or trough ITD functions that share the essential features of responses in the MSO and LSO (e.g., Yin and Kuwada 1983b). Some ICC units show temporal response patterns that are neither peak nor trough type (Batra et al. 1993; Kuwada et al. 1987). These “intermediate units” are not predicted by the classic input coincidence detection model of Jeffress (1948) and may be created by combining peak and trough type brain stem inputs within the ICC (McAlpine et al. 1998; Yin and Kuwada 1983b) or by local processing effects (McAlpine and Palmer 2002) may simply reflect the heterogeneity of brain stem responses (Batra et al. 1997; Fitzpatrick et al. 2002).

The present study measures the ITD sensitivity of single-unit responses in the ICC of decerebrate cats. Because the effects of anesthesia and descending efferent innervation are eliminated by the decerebration procedure, this experimental design provides an excellent context for isolating brain stem sources that influence binaural temporal processing in the auditory midbrain. In addition, these measures provide another metric for

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linking ICC response types in decerebrate cats to input sources that have been suggested by our previous work (Davis 2002; Davis et al. 1999; Ramachandran et al. 1999, 2000).

More than 90% of the single-unit responses in the ICC of decerebrate cats exhibit sustained discharge rates during presentations of contralateral tones (Ramachandran et al. 1999). The remaining neurons show a brief burst of activity at stimulus onset. Neurons with sustained discharge rates can be divided into three basic response types based on the patterns of excitation and inhibition that are elicited when the tone is changed in frequency and level. Type V frequency-response maps are exclusively excitatory (BF: the most sensitive frequency) that is flanked by inhibition (Fig. 1A). Type I maps are defined by a narrow I-shaped excitatory area at best frequency (BF: the most sensitive frequency) that is flanked by inhibition (Fig. 1B). Type O maps are largely inhibitory except for an O-shaped island of excitation near the BF threshold (Fig. 1C).

Type V, I, and O units exist in the ICC of decerebrate cats and therefore do not manifest descending efferent influences. The physiological classification of ICC neurons is not strongly modified by local pharmacological manipulations (Davis et al. 1999). These observations have led to the speculation that ICC response types represent parallel information processing pathways that are created in the different nuclei of the auditory brain stem and remain functionally segregated in the midbrain. Based on similarities in frequency-response map features, Ramachandran et al. (1999) ascribed the respective sources of ascending input to type V, I, and O responses as the MSO, LSO and dorsal cochlear nucleus (DCN). Davis et al. (1999) added to this parallel processing model by showing a similar correspondence in the binaural properties of the ICC response types and their putative sources of ascending inputs. More recently, Davis (2002) demonstrated that most type O units in the ICC are silenced when the tectal projections of the DCN are disrupted with surgical or pharmacological manipulations of the dorsal acoustic stria.

Our interpretations of single-unit responses in decerebrate cats envision ICC neurons as highly selective integrators. That is, the discrete properties of each response type is attributed to a single source of ascending input dominating a potentially rich and diverse convergent innervation. This reductionist view is not meant to imply that additional sources of ascending input, local processing networks, or descending efferent projections do not contribute to neural responses in the ICC. Instead, the parallel processing model is intended to provide a heuristic for isolating the lower-order inputs that give rise to the functional identity of ICC response types. This information is a prerequisite for understanding how ascending inputs are acted on by the complex serial/parallel processing pathways of the nucleus.

Our present study investigates the ITD sensitivity of single-unit activity in the ICC of decerebrate cats. As predicted by the parallel processing model, type V and I units mirrored their putative MSO and LSO inputs by showing characteristic delay responses of the peak and trough type. Most type O units were insensitive to interaural phase, which is consistent with a weakly binaural input from the DCN. Local processing effects also were implied by type I units that produced intermediate ITD functions and type O units that exhibited an enhancement of binaural temporal sensitivity. In addition to providing further support for our parallel processing model of the ICC, these results suggest that the temporal pathways of the ICC are endowed with the capacity to encode ITD information by response patterns that are inherited from their brain stem inputs. The close correspondence of our findings in decerebrate cats with previous results in anesthetized animals is strong evidence that these temporal processes are not radically altered by the effects of anesthesia or the elimination of descending efferent influences.

**METHODS**

All experimental procedures in this report were approved by the Institutional Animal Care and Use Committee of Johns Hopkins University.

**Surgical procedures**

Surgical procedures for acute single-unit recording in the ICC of decerebrate cats have been described in detail in previously published work (Davis 2002; Davis et al. 1999; Ramachandran et al. 1999, 2000). Briefly, adult cats (3–4 kg) were anesthetized with xylazine (2 mg im) and ketamine (initial dose 40 mg/kg im; supplemental doses 15 mg/kg iv), and then decerebrated by aspirating through the brain stem rostral to the superior colliculus. Anesthesia was discontinued until the experiment was terminated by an intravenous injection of pentobarbital sodium (26 mg/kg iv). The completeness of the decerebration procedure was indicated during experiments by a lack of voluntary movements and verified after experiments by visual inspection of the perfused brain. The ICC was exposed by aspirating occipital cortex and removing the inferior tentorium. The head was secured by a stereotaxic apparatus in a standard horizontal orientation.
to facilitate a dorsal electrode approach to recording sites in the ICC. The entry point of the electrode track was determined by visual confirmation of surface features.

Closed-field acoustic system

Experiments were conducted inside a sound-attenuating chamber. Acoustic stimuli were delivered bilaterally via electrostatic speakers that were coupled to hollow ear bars. Signal presentation levels were calibrated at the beginning of each experiment by inserting a probe microphone into the ear bar near the tympanic membrane. The response of the closed-field sound delivery system was uniform to within \( \pm 5 \) dB at frequencies from 40 Hz to 40 kHz. Applying equal attenuation to binaural tones of the same frequency produced an output that was equivalent to within \( \pm 2 \) dB at the two ears.

Recording protocol

Single-unit activity was recorded with platinum-iridium electrodes. The electrode signal was amplified (\( \times 10,000 - 30,000 \)) and low-pass filtered at 6 kHz. A variable-threshold Schmitt trigger was used to discriminate action potentials from background activity.

Electrodes were advanced dorsoventrally through the ICC with a hydraulic micromanipulator. The electrode track passed through the external or dorsal nucleus before entering the ICC (Aitkin et al. 1975; Merzenich and Reid 1974). The transition between subdivisions was indicated by a reversal in the trend of BFIs for single-unit or multiunit activity.

Well-isolated ICC units with sustained discharge rates were classified as a type V, I, or O according to their responses to contralateral and ipsilateral stimuli. First, BF was determined by finding the tone frequency that elicited sound-evoked activity at the lowest presentation level. Then frequency-response maps were constructed from the unit's responses to fixed-level frequency sweeps. Each sweep began at BF and was allowed to progress toward more remote frequencies until tone-driven activity ceased. Excitatory and inhibitory frequency responses were characterized at approximately six presentation levels, as shown in Fig. 1.

After unit classification, ITD responses were measured with binaural stimuli that differed in frequency by 1 Hz at the ears. This frequency difference leads to dynamic ITD changes that cycle at a rate of 1 Hz and impart a perceptual “beat” (Kuwada et al. 1979). Units with low BFs (\(< 3 \) kHz) were studied with pure tones that ranged in frequency from 0.05 to 2 kHz in steps of 50 Hz. Units with high BFs (\( > 3 \) kHz) were studied with sinusoid amplitude-modulated (SAM) tones or noise carriers. The carrier tone was placed at the unit's BF. The modulation tone ranged in frequency from 25 to 950 Hz in steps of 25 or 50 Hz. Each frequency condition was repeated at least four times. Tests at different frequencies were interleaved to minimize the effects of time-dependent variations in response rates or unit isolation.

Binaural beats were presented for 3.1 s with a silent interval of 2 s between successive stimuli. This stimulus duration presented multiple beats. Initial tests were conducted at presentation levels \( -10 \) dB re threshold, which is an effective stimulus condition for evoking excitatory discharge rates from even the largely inhibitory type O responses. Additional tests were performed at \( +40 \) dB re threshold if isolation was maintained.

Analysis of ITD sensitivity

The analysis of responses to binaural beats is summarized in Fig. 2. Responses to binaural beats and extraction of mean phase for a low-BF type V unit (A, C, and E), and a high-BF type I unit (B, D, and F). Units are the same as those shown in Fig. 1. A and B: peristimulus time histograms (PSTHs) for responses to binaural beat stimuli that were 3.1 s in duration and repeated at a rate of 1 Hz. C and D: period histograms obtained from the last 2 s of the PSTHs. Discharge rates have been folded into 1 period of the binaural beat (1 s) and are plotted as a function of phase. E and F: the 1-Hz component of the fast Fourier transform (FFT) of the period histograms is superimposed on the magnitude of the period histograms. \( \downarrow \), the phase at which the maximum peak of the 1-Hz component occurs (mean phase). In all cases, binwidth was 10 ms.

The amplitude and phase of the maximum response to a binaural beat was determined by performing a fast Fourier transform (FFT) on the period histogram and then calculating the phase of the 1-Hz component in the FFT. The results of this analysis are presented as \( \rightarrow \) in Fig. 2, E and F. The outline of the period histograms in Fig. 2, C and D, are also shown to illustrate how the FFT analysis provides an estimate of the best sinusoid fit to actual data. If the fit indicated a statistically significant synchronization to the binaural beat (Kuwada et al. 1987), the phase of the maximum response was accepted as the “mean phase” of the tone or modulation frequency. In this example, the type V and I units exhibited respective mean phase values of 0.1 and 0.5 cycles (\( \downarrow \)).
When an auditory neuron is sensitive to the interaural phase of binaural beats and encodes a unique binaural time difference, the phase of the response changes linearly with the frequency of the binaural beat. ITD response type and delay tuning are fully described by this relationship. The analysis of linear ITD sensitivity is conducted by measuring the effects of stimulus frequency on mean phase as described in RESULTS.

RESULTS

The following results are based on 79 ICC units from eight decerebrate cats. This sample was approximately equally divided among units with BF < 3 kHz (10 type V, 22 type I, and 14 type O) and units with BF > 3 kHz (11 type I and 22 type O). As in our previous studies (Ramachandran et al. 1999), no type V units were observed at BF > 3 kHz.

Approximately one-half of the units in the sample (n = 37/79) failed to show ITD sensitivity. Both responsive and nonresponsive units are relevant for our interpretations of the functional segregation of ITD sensitivity in the ICC. The relatively small sample of responsive units is sufficient to relate our system of physiological classification to patterns of ITD encoding that have been more fully described in anesthetized preparations. These comparisons provide direct evidence that temporal sensitivity to binaural beats is not strongly modified by the effects of anesthesia or decerebration. The distribution of response patterns for each unit type is summarized in Table 1.

Responses of low-BF units to binaural tone beats

Units with BF < 3 kHz were primarily tested with binaural tone beats. The ITD functions of representative units from each ICC response type are shown in Fig. 3, left. For the clarity of illustration, results are compared for only a subset of the 10–14 carrier tone frequencies that were used to evaluate the ITD sensitivity of each unit.

The effects of carrier frequency on the discharge rates of a type V unit are summarized in Fig. 3A. This is the same low-BF unit that was used to describe type V frequency-response maps in Fig. 1 and the mean phase analysis in Fig. 2. Although the overall discharge rates of the unit were strongly influenced by frequency, each ITD function attained its maximum response when the binaural time disparity neared 100–150 μs. The convergence of ITD functions at their maximum rates is characteristic of peak type responses that have been previously associated with MSO neurons.

![Figure 3](http://jn.physiology.org/)

**Fig. 3.** Typical patterns of interaural time difference (ITD) sensitivity for low-BF type V (A and B), type I (C and D), and type O units (E). Left: rate responses are plotted in relation to the dynamic ITD of binaural beats. Individual lines represent responses at different carrier frequencies. Right: the mean phase values of the responses are plotted in relation to carrier frequency. When the phase-frequency relationship is linear, the unit’s characteristic phase (CP) is indicated by the y intercept of the function (∼ in B and D). The unit’s characteristic delay (CD) determines the slope of the function (↓ in A and C). These measures are not presented for the type O unit because it failed to show temporally structured responses.

Mean phase values for the type V unit’s complete set of ITD functions are presented in Fig. 3B. At each of the 10 stimulus conditions (○), mean phase increased in proportion to carrier frequency. These results produced a statistically significant linear correlation when a weighted least-squares fit was applied to the data. The synchronization index at each frequency was used as the weight for these calculations to bias the analysis toward frequency conditions where the unit exhibited higher and more synchronized discharge rates (Yin and Kuwada 1983a,b).

A linear phase-frequency relationship suggests that a binaural neuron is responding to the same ITD under different frequency conditions. This “characteristic delay” (CD) is indicated by the change in mean phase with carrier frequency and therefore is estimated by the slope of the linear fit (Kuwada et al. 1987). The phase-frequency data of the type V unit in Fig. 3B indicate a CD of 115 μs. This value corresponds to the coincident peak delay in Fig. 3A (∼).

The peak versus trough classification of an ICC unit is based on the presence of an invariant phase relationship at the CD. This measure is termed the characteristic phase (CP) of the multiple frequency ITD functions. Ideal peak type units respond best to in-phase binaural inputs, which are indicated by CP values near 0 cycles of the binaural beat. Conversely, trough type units are most active for the anti-phase stimuli conditions that are associated with CP values near 0.5 cycles.

<table>
<thead>
<tr>
<th>BF Range</th>
<th>ICC Unit Type</th>
<th>No. of Units</th>
<th>ITD-Sensitive Units</th>
<th>Insensitive Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BF</td>
<td>V</td>
<td>10</td>
<td>P 4 I 4 T 0 NL 2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>22</td>
<td>2 9 3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>14</td>
<td>2 4 0 0</td>
<td>8</td>
</tr>
<tr>
<td>High BF</td>
<td>I</td>
<td>11</td>
<td>0 1 3 0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>22</td>
<td>4 1 2 0</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>79</td>
<td>12 19 8 3</td>
<td>37</td>
</tr>
</tbody>
</table>

P, peak type (0 ≤ CP ≤ 0.1, or 0.9 ≤ CP ≤ 1); T, trough type (0.4 ≤ CP ≤ 0.6); I, intermediate type (0.1 < CP < 0.4, or 0.6 < CP < 0.9); NL, nonlinear phase-frequency relationship; ICC, inferior colliculus; ITD, interaural time difference; BF, best frequency.
The CP of a binaural neuron is estimated from the y intercept of the linear fit to the phase-frequency function. When this analysis was applied to the data in Fig. 3B, a CP of 0.03 cycles confirmed the peak-type ITD responses of the type V unit.

The ITD functions of a low-BF type I unit are shown in Fig. 3C. Although a coincident trough is clearly evident in this example, objective classification of the unit was based on an analysis of mean phase values at different carrier frequencies. This phase-frequency relationship is presented in Fig. 3D. The slope of the linear fit to the data estimated a CD of ~96 µs (Fig. 3C, ↓). The y intercept of the fit indicated an anti-phasic CP of 0.61 cycles (Fig. 3D, ←). Consequently, the ITD sensitivity of the type I unit was designated trough type.

The ITD functions of a low-BF type O unit are shown in Fig. 3E. Like the unit in this example, more than half of the low-BF type O units (n = 8/14) failed to exhibit temporally structured ITD sensitivity. The absence of consistent rate peaks in the ITD functions made it impossible to calculate meaningful mean phase values for the different carrier frequencies. No analysis of CP or CD was attempted for the unit.

The examples in Fig. 3 represent the discrete patterns of ITD sensitivity that are predicted by our parallel processing model of brain stem inputs to type V, I, and O units. These response types were commonly observed for low-BF units, but not all units showed expected patterns of ITD sensitivity. Some alternative response types are presented in Fig. 4.

A low-BF type V unit displays mixed ITD sensitivity in Fig. 4, A and B. That is, the individual ITD functions have sufficient temporal structure to allow the calculation of mean phase but neither peak nor trough rates coincide at any point in time. The lack of a consistent ITD effect produces a nonlinear phase-frequency relationship without characteristic phase or delay values. These results suggest that the unit does not encode a static ITD but rather integrates convergent inputs with differing ITD sensitivity (e.g., McAlpine et al. 1998). This type of temporal sensitivity may be important for processing dynamic ITD cues that are associated with relative motion between the observer and the sound source. Nonlinear phase-frequency functions were relatively uncommon in our study of decerebrate cats (n = 3/42).

Low-BF units often displayed phase-frequency relationships that were linear but could not be classified according to peak versus trough responses. The ITD functions for a so-called “tweener” type I unit are shown in Fig. 4, C and D. The unit produced a CP of 0.29 cycles, which is intermediate to ideal peak and trough responses. Notwithstanding this ambiguity of response type, the linear nature of the phase-frequency relationship indicates the coincident responses at the rising phase of the ITD functions were evoked by an invariant time delay of 24 µs.

The ITD functions of a low-BF type O unit display temporally structured responses to binaural beats in Fig. 4, E and F. Analysis of the resulting linear phase-frequency relationship produced a conventional peak-type CP of 0.03 cycles. The unit’s CD was 97 µs. Type O units with peak or intermediate ITD functions typically showed excitatory responses when tested with monaural ipsilateral tones. This binaural interaction suggests that the discharge rates of a subset of type O units are temporally modulated by ascending MSO inputs that are independent of the contralateral DCN.

Responses of high-BF units to binaural SAM beats

Units with BFs >3 kHz were tested with binaural beats that were created by sinusoidally modulating the amplitude envelope of broadband noise. Most high-BF units (n = 22/33) failed to produce temporally structured ITD functions when tested with binaural SAM beats. The remaining units exhibited patterns of ITD sensitivity that were similar to previous descriptions of single-unit activity in the ICC (e.g., Batra et al. 1989; Yin et al. 1984). The trough-type ITD functions of a temporally sensitive type I unit are shown in Fig. 5, A and B. The CP of this unit was 0.49 cycles with a CD of 17 µs. Trough responses were the most common ITD structure for high-BF type I units.

Most high-BF type O units with linear ITD sensitivity displayed peak responses (n = 4/7), but trough responses were also observed (n = 2/7). Results from a type O unit with peak responses are shown in Fig. 5, C and D. The type O unit in this example had a CP of 0.04 cycles and a CD of ~5 µs. For comparison, the trough-type ITD functions and phase-frequency data of another type O unit are presented in Fig. 5, E and F. This unit produced a CP of 0.49 cycles and a CD of ~45 µs.

Distribution of characteristic phase across unit types

The distribution of CP values across ICC unit types was evaluated to gain additional insights regarding the potential sources of ascending input that influence ITD sensitivity. Figure 6 shows the CP distribution of all type V, I, and O units that displayed linear phase-frequency functions and therefore un-
ambiguous CP values. No obvious effects of BF were evident in this analysis, and data from low- and high-BF units have been combined to increase the number of observations within each distribution. The cycle of CP scores has been “wrapped” at values \(0\) and \(0.5\) to create a single continuum of peak to trough responses.

Each unit type displayed a range of CP values that was broadly predicted by our parallel processing model. Type V units exhibited the most compact distribution. Of the eight linear units in this response class, four units produced MSO-like peak ITD functions and no units showed trough responses. The CP distribution of the 19 linear type I units was biased toward LSO-like trough functions, but peak and intermediate responses also were observed among high-BF units. An unexpected outcome was the identification of possible MSO influences on type O units. Eleven of the 13 linear type O units exhibited peak or intermediate ITD sensitivity. Only two units displayed trough responses. Most type O units were insensitive to binaural beats \(n = 23/36\) as expected for the midbrain targets of DCN projections.

**Distribution of characteristic delay across unit types**

The distribution of CD values across unit types reveals the range of binaural time delays that are most frequently encoded within the ICC. Because CD is derived from the slope of phase-frequency functions, this analysis is limited to the subset of units in our sample that displayed linear phase-frequency relationships. Positive CDs indicate a temporal tuning to binaural sounds with ipsilateral delays, which are associated with contralateral sound sources in free field. Conversely, negative CDs reflect ipsilateral spatial coordinates.

The stacked histograms in Fig. 7A show the distribution of CD for low-BF units. The majority of the units produced CD values that fell between \(\pm 500\ \mu s\). This range corresponds well with the natural diversity of ITD information that has been described in acoustic studies of cats \((- - -\) (Roth et al. 1980). Within these biological limits, type I and O units provided an approximately equal representation of positive and negative CDs. Type V units exhibited a contralaterally dominant ITD sensitivity. The combined CD distribution of all three unit types suggests an enhanced representation of time delays near \(0\ \mu s\).

The CD distribution of high-BF units is presented in Fig. 7B. Although a relatively small number of high-BF units produced linear phase-frequency relationships, the resulting distribution shows essentially the same properties as the more densely sampled low-BF distribution.

![FIG. 5. Typical ITD and phase-frequency functions for high-BF units with linearly structured responses to binaural sinusoid amplitude-modulated (beats). The response map of the type I unit in this example is shown in Fig. 1B. See Fig. 3 for a description of plotting conventions.](image)

![FIG. 6. CP distributions for type V, I, and O units. BF ranges are indicated by shading patterns. Dashed lines separate peak, intermediate, and trough responses. CP values between 0 and 1 have been wrapped at 0.5 cycles to emphasize peak vs. trough sensitivity.](image)
Effects of stimulus level on ITD sensitivity

Inhibitory effects are pervasive in the ICC of decerebrate cats. In particular, type O and I units are strongly inhibited by most combinations of frequency and level (Fig. 1). The probability of eliciting excitatory responses during the cycle of binaural beats was maximized by conducting most tests at a 10 dB re threshold stimulus level. This is a relatively quiet presentation in comparison to previous measures of ITD sensitivity. To confirm that the ITD sensitivity of our sample was not grossly underestimated by our choice of stimulus level, some units also were tested with 40 dB re threshold binaural beats. Figure 8A contrasts the CP values of 10 low-BF units at 10 versus 40 dB re threshold. In most instances, the data fall along the unity line, indicating no effect of stimulus level. Stimulus level also had no effect on eight low-BF units that did not show ITD sensitivity for testing at 10 dB re threshold and remained insensitive at the higher testing level (data not shown). Two type O units exhibited peak and intermediate ITD response patterns at the low stimulus level but became nonlinear at the higher level. One type V unit with nonlinear responses at the low stimulus level was transformed to linear peak-type responses at the higher level. These nonlinear responses are plotted along the x and y axes of the figure.

Level-tolerant CP values, and therefore stable ITD response types, also were observed when eight high-BF units were tested at 40 dB re threshold. These results are shown in Fig. 8B. The bias toward type O peak responses and type I trough responses is made clear by the clustering of units near CPs of 0 and 0.5 cycles. Eight high-BF units were insensitive to ITD at both 10 and 40 dB testing levels (data not shown).

The effect of stimulus level on CD is summarized in Fig. 8, C and D. A similar insensitivity to the change in stimulus level is indicated by the symmetrical scattering of the data along the unity line. In this plotting format, the abundant representation of delays that correspond to spatial locations in the immediate frontal field is indicated by the clustering of responses near 0 μs.

FIG. 7. CD distributions for low-BF (A) and high-BF units (B). Type V, I, and O units are distinguished by shading patterns. - - -, the maximum biological range of ITD information in cats (±435 μs) (Roth et al. 1980).

DISCUSSION

ICC units in our study of decerebrate cats replicated patterns of activity that have been previously described in anesthetized preparations. These results are significant because they suggest that binaural temporal processing is not radically altered by the effects of anesthesia or the surgical elimination of descending efferent projections to the auditory midbrain. When these generalized patterns of ITD sensitivity are interpreted in the context of physiologically defined response types, the major finding of the present study is that temporal processing in the ICC appears be determined by functionally segregated pathways that originate in the auditory brain stem. Type V and I units
tend to show peak and trough responses that suggest functional links with the superior olive. Most type O units are insensitive to binaural temporal cues like their presumed DCN inputs. Nevertheless, each response type exhibits unexpected patterns of binaural sensitivity that may reflect processing enhancements for ITD-encoding within the ICC.

**Comparisons with previous studies of ITD sensitivity**

Binaural beats are frequently used in physiological studies of ITD processing because they provide a rapid assessment of the importance of interaural phase relationships that are implied by the coincidence detection model (Kuwada and Yin 1983). It is well known that absolute phase tuning of ICC neurons may change under static versus dynamic (binaural beat) protocols because the response to a particular phase difference is influenced by preceding aspects of the time-varying stimulus (Spitzer and Semple 1993). This sensitivity to simulated sound motion increases in the ICC relative to the superior olivary complex (Spitzer and Semple 1998) and may arise from adaptation effects that are modulated by local inhibitory mechanisms (McAlpine and Palmer 2002). Our experiments have maintained the traditional binaural beat approach because it allows the most comprehensive comparisons of our present results with previous studies of ITD sensitivity.

Most ITD-sensitive neurons (n = 39/42) showed linear phase-frequency relationships in the present study. Approximately one-half of these neurons produced CP values that fell between ideal peak and trough responses and therefore are not predicted in a straight-forward manner by the Jeffress coincidence model. The increased prevalence of intermediate units in the ICC has been previously explained by proposing convergence among linear SOC neurons with different BFs or CDs (McAlpine et al. 1998; Yin and Kuwada 1983a) or by the existence of nonlinear inputs from the brain stem (Fitzpatrick et al. 2000). Our current findings add little resolution to this contemporary debate but do imply that intermediate ITD sensitivity is created by a mechanism that is not radically altered by anesthetic agents or descending efferent influences.

The description of linear ITD effects in our study is biased toward results that were obtained from units with BFs <3 kHz (n = 28/39). Important differences may exist between these low-BF units and the high-BF units that also contributed to the CP distribution in Fig. 6. For example, few low-BF units produced CP values that were classified as LSO-like trough type responses (~10%). Similar results have been previously reported in anesthetized cats (Yin and Chan 1990; Yin and Kuwada 1983a,b) and awake rabbits (Kuwada et al. 1987). Trough type units are common at low BFs in the LSO (Batra et al. 1997; Finlayson and Caspary 1991), but these inferences may be diminished in the ICC because only about one-half of the ICC projections from the lateral limb of the LSO are excitatory (Oliver et al. 1995; Saint Marie et al. 1989). The majority of low-BF units exhibited intermediate CP values (~60%) and not the expected MSO-like peak type responses. An increase in intermediate responses relative to MSO distributions is also observed at low BFs in anesthetized cats (Yin and Chan 1990).

Most high-BF type I and O units showed ideal peak or trough type responses (~80%). This more categorical high-frequency ITD sensitivity has been observed in the ICC of awake rabbits (Batra et al. 1993). Ultimately, the absolute percentage of units that is assigned to each ITD response type is determined by the criteria that are used to distinguish canonical peak and trough responses from a broader range of intermediate CP values. The present study follows the conservative conventions used by McAlpine et al. (1998).

The CD distributions in Fig. 7 are skewed toward positive values and therefore suggest a contralateral dominance for ITD sensitivity in the ICC. Similar effects have been noted in previous ITD studies (Kuwada et al. 1987; McAlpine et al. 1998) and in free-field investigations of directional sensitivity in the ICC (Jenkins and Masterton 1982; Kelly and Kavanagh 1994; Strominger and Osterreich 1970). The distributions in Fig. 7 also reveal an over-representation of CDs between ±200 μs. Delays of this magnitude are produced in cats when sound source azimuths are located within ±45° of the median plane (Roth et al. 1980). Behavioral studies have shown that cats display their most accurate directional acuity within this range of sound locations (Casseday and Neff 1973; Heffner and Heffner 1988; Huang and May 1996; Martin and Webster 1987).

Our interpretation that ITD sensitivity in the ICC is capable of supporting accurate sound-localization behavior is constrained by the limited range of stimulus conditions in the present study. The majority of our electrophysiological measures were conducted near threshold and not the moderate listening levels that are used in most behavioral assessments of directional hearing. Results in Fig. 8, C and D, suggest CD values do not change radically at higher sound levels. Any conclusions drawn from this small sample must be made with caution because more detailed studies have previously reported level dependencies for delay sensitivity (Kuwada et al. 1987; Yin and Kuwada 1983).

**Parallel processing pathways in the ICC**

Our hypothesized parallel pathways model provides a theoretical context for isolating the multiple ascending inputs that shape ITD processing in the ICC. This functional segregation is facilitated by the distinct ITD response patterns of the primary nuclei of the auditory brain stem. The cochlear nucleus shows only weakly binaural responses (Mast 1970; Pfalz 1962; Young and Brownell 1976). The superior olive is the first site of the profuse binaural interactions that establish clear ITD sensitivity in single-unit responses (Batra et al. 1997; Goldberg and Brown 1969; Joris 1996; Joris and Yin 1995; Spitzer and Semple 1993; Yin and Chan 1990). Candidate sources of olivary input to the ICC can be further distinguished by the tendency of MSO units to show peak type responses to binaural beats (Batra et al. 1997; Joris 1996; Yin and Chan 1990); whereas, LSO units typically show trough type responses (Batra et al. 1997; Spitzer and Semple 1995).

Type V units display broad excitatory frequency-response maps when tested with contralateral or ipsilateral tones (Ramachandran et al. 1999) and exhibit excitatory binaural interactions (Davis et al. 1999). The frequency tuning of type V units is biased toward low BFs (Ramachandran et al. 1999). This constellation of response properties parallels the basic characteristics of MSO neurons (Batra et al. 1997; Goldberg and Brown 1969; Yin and Chan 1990) and has led to the hypothesis...
that type V units receive their dominant inputs from the MSO (Ramachandran et al. 1999).

ITD measures from the small sample of type V units in the present study provide further support for the existence of an MSO/type V pathway. All type V units showed interaural phase sensitivity to binaural beats. Subsequent analysis of CP values classified one-half of the resulting ITD functions as MSO-like peak responses (Fig. 6). No type V units produced LSO-like trough responses. In addition, the ITD functions of type V units are biased toward positive CDs and therefore contralateral sound sources (Fig. 7A). MSO units also preferentially encode contralateral space (Batra et al. 1997; Yin and Chan 1990).

Some linear type V units produced intermediate ITD functions. Other units displayed nonlinear phase-frequency relationships. Such deviations from peak responses are observed in the MSO and its vicinity in awake rabbits (Batra et al. 1997). Although this variation is less apparent in acute studies of the MSO where more accurate localization of the recording site is ensured (Joris et al. 1996; Yin and Chan 1990), low-BF ICC neurons in anesthetized cats also show an increased prevalence of intermediate responses relative to MSO neurons (Yin and Chan 1990). Consequently the observed range of CP values for type V units in decerebrate cats may partially reflect variations in the ITD sensitivity of MSO inputs but is more likely to be augmented by the interactions of ITD-sensitive inputs from the superior olive and local processing effects (McAlpine and Palmer 2002; McAlpine et al. 1998).

Type I units are presumed to reflect inputs from the contralateral LSO. They are excited by a narrow range of frequencies around BF and inhibited by a wide range of flanking frequencies when tested with contralateral tones (Ramachandran et al. 1999). Ipsilateral frequency-response maps and binaural interactions are largely inhibitory (Davis et al. 1999; Ramachandran et al. 1999). These properties previously have been attributed to LSO units (Boudreau and Tsuchitani 1968; Caird and Klinke 1983; Tsuchitani and Boudreau 1969). Among the low-BF units in the present study, only type I units exhibited LSO-like trough responses.

Type I units were found to display a greater range of CP values than their type V counterparts in our sample of low-BF units (Fig. 6). The majority of linear type I units exhibited intermediate or peak responses. A substantial proportion of units failed to show linear responses or even temporal sensitivity. Again, because the ITD responses of low-BF LSO units are diverse (Batra et al. 1997), these results may simply reflect the normal variation of LSO inputs to the ICC. Type I units in our sample were inhibited by ipsilateral stimuli, which is consistent with the predicted influences of an LSO projection.

The range of linear high-BF type I units was limited to trough or near-trough responses in the minority of cases where the units exhibited ITD sensitivity (Fig. 6). Previous studies have noted a similar shift toward more categorical responses for high-BF neurons in the superior olive (e.g., Batra et al. 1993). Although this manner of ITD coding is expected for the midbrain targets of LSO projections, the majority of high-BF type I units were unresponsive to ITD changes in the context of SAM tones or noise, and at both low and high presentation levels.

The presence of numerous ITD-insensitive units spanning a range of low and high BFs implies elements of the type I response class are created independently of LSO projections, perhaps from monaural inputs that originate in the cochlear nucleus (Oliver 1987). A creation de novo of the frequency-response map features of type I units from cochlear nucleus projections must occur before the ascending neural representation reaches the ICC because type I response maps are not strongly altered by local pharmacological manipulations (Davis et al. 1999). Alternatively, ITD-insensitive type I units may reflect a more selective modification of superior olivary inputs that is not responsive to binaural beats. Neither possibility is ruled out by our present results.

Type O units are strongly inhibited by most combinations of frequency and level when stimuli are presented to the contralateral ear (Ramachandran et al. 1999). Units in this response class tend to be weakly binaural and display ipsilateral frequency-response maps and binaural interactions that are almost exclusively inhibitory. Similar response patterns have been described for the type IV projection neurons of the DCN (Spirou and Young 1991; Young and Brownell 1976), which have been proposed as the dominant brain stem input to type O units (Ramachandran et al. 1999).

Pharmacological manipulations provide the most direct evidence for functional links between the DCN and ICC type O units. Blockade of GABAAergic inhibition within the ICC by local administration of bicuculline fails to modify the defining characteristics of frequency-response maps for most type O units (Davis 2002; Davis et al. 1999). By contrast, most type O activity is reversibly silenced when lidocaine is used to block neurotransmission in the output pathways of the DCN (Davis 2002).

Our parallel processing model predicts a lack of ITD sensitivity for type O units because their putative DCN inputs are minimally responsive to binaural stimuli (Mast 1970; Young and Brownell 1976). Consistent with this interpretation, ~65% of the low- and high-BF type O units failed to show temporally structured responses when tested with binaural beats.

A number of type O units did display surprisingly good ITD sensitivity that is not readily explained in terms of DCN inputs. Among the low-BF type O units, ITD-sensitive neurons produced MSO-like peak or near-peak ITD functions and never showed trough responses when tested with low-level binaural beats (Fig. 6). Some low-BF type O frequency-response maps can be converted into type V responses by blocking local GABAergic inhibition with bicuculline (Davis et al. 1999). The mutable type O units from our previous work and the ITD-sensitive type O units in the present study may reflect the same pattern of binaural inputs because both subclasses exhibit an excitatory response to ipsilateral tones that is more commonly associated with MSO inputs to type V units. In addition, the phase-frequency functions of the low-BF type O units tend to become nonlinear at high levels (Fig. 8A); this relationship suggests a convergence of multiple ITD-sensitive inputs (McAlpine et al. 1998; Yin and Kuwada 1983b). The general agreement of the CP distributions of low-BF type O units and type V units is further evidence that the binaural sensitivity of both unit types is determined by inputs from the MSO (Fig. 6).

ITD-sensitive type O units with high BFs also were biased toward peak type responses. These units may reflect excitatory inputs from high-BF peak neurons in the MSO or may be derived from trough type LSO neurons that shape the temporal structure of type O responses through inhibitory inputs. This
latter interpretation is supported by the essentially opposite polarity of CP values for high-BF type O and I units (Fig. 6).

An anatomical basis for the integration of inputs from the superior olive and DCN is supported by the existence of LSO inhibitory projections to ICC regions that are preferentially targeted by the DCN (Oliver et al. 1997). In addition to direct inhibitory inputs from the ipsilateral LSO (Glendenning and Masterton 1983; Glendenning et al. 1992), ITD-sensitive inputs from both the LSO and MSO may indirectly influence the ICC by way of inhibitory projections from the dorsal nucleus of the lateral lemniscus (DNLL) (see Schwartz 1992).

Our study of ITD sensitivity was guided by the concept of parallel information-processing pathways that can be identified by the presence of discrete physiological response types in the ICC of decerebrate cats. It was hypothesized that type V and I units would show temporally structured responses to binaural beats because these unit types reflect pathways that are established in the superior olive and remain functionally segregated in the ICC. General patterns of ITD coding in the ICC support these predictions. Additional results suggest a convergence of cochlear nucleus and olivary inputs. Many type O units display binaural temporal tuning that is not predicted by discrete inputs from the DCN. Although type I units are expected to show LSO-like trough sensitivity, the majority of these units exhibited unexpected peak, intermediate, nonlinear, or insensitive responses to binaural beats. In instances of both expected and unexpected outcomes, the parallel pathways model has proven to be a useful construct for isolating the ITD-sensitive projections that converge on the ICC and interpreting how these sources of input may be modified by local processing effects.

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